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Attention deficit hyperactivity disorder, physical abuse and methylphenidate treatment in children

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A growing number of studies show an association between attention deficit hyperactivity disorder and physical abuse in childhood. We examined temporal associations of physical abuse risk with methylphenidate treatment in children with attention deficit hyperactivity disorder. Using Hong Kong electronic medical records, we conducted a self-controlled case series study in 1,064 children (5–16 years old) who were treated with methylphenidate and also experienced physical abuse. Compared with non-medicated periods, a higher risk of abuse was observed shortly before treatment initiation (incidence rate ratio = 4.49; 95% confidence interval = 3.76–5.36). After treatment initiation, the risk was comparable to that in non-medicated periods (incidence rate ratio = 0.90; 95% confidence interval = 0.63–1.29), followed by a 37% reduction during subsequent treatment. These findings are consistent with the hypothesis that methylp henidate treatment in children with attention deficit hyperactivity disorder is associated with a reduced risk of becoming a victim of physical abuse.

Physical abuse in childhood is common, with about 25% of adults reporting that they were physically abused as children[1,2]. The consequences of child abuse include impairments to physical and mental health that can extend into adulthood, ultimately affecting social and economic development[2]. Childhood physical abuse is considered an important risk factor for depressive disorders in adulthood[3]. Previous research has shown that abuse resulted in a 2.3-fold increase in hospitalization between 2001 and 2010 in Hong Kong, with recorded cases in 2010 at 7.3 per 10,000 children under 19 years old[4].

Children with attention deficit hyperactivity disorder (ADHD) are at higher risk than their peers of being victims of abuse, particularly physical abuse[5–9]. Multiple factors may contribute to this increased risk. As ADHD is highly heritable and has shared genes with other psychopathologies[10,11], many parents of children with ADHD also suffer from ADHD and other psychopathologies including depression, which could potentially increase the risk for negative and suboptimal parenting practices as well as perpetrating abuse[10]. Harsh parenting is also associated with an increased interactive aggravation of ADHD and oppositional symptoms in the child. In addition, many parents find parenting a child with ADHD challenging, particularly when ADHD is untreated[12]. Children with untreated ADHD may push boundaries laid down by adults, and such behaviours may be viewed as disobedient and wilful, further increasing parental stress and creating a cycle of escalating negative parent and child behaviours[8,13] with serious consequences including domestic violence/abuse and child abuse[14]. Here, it is important to note that when one individual perpetrates abuse on

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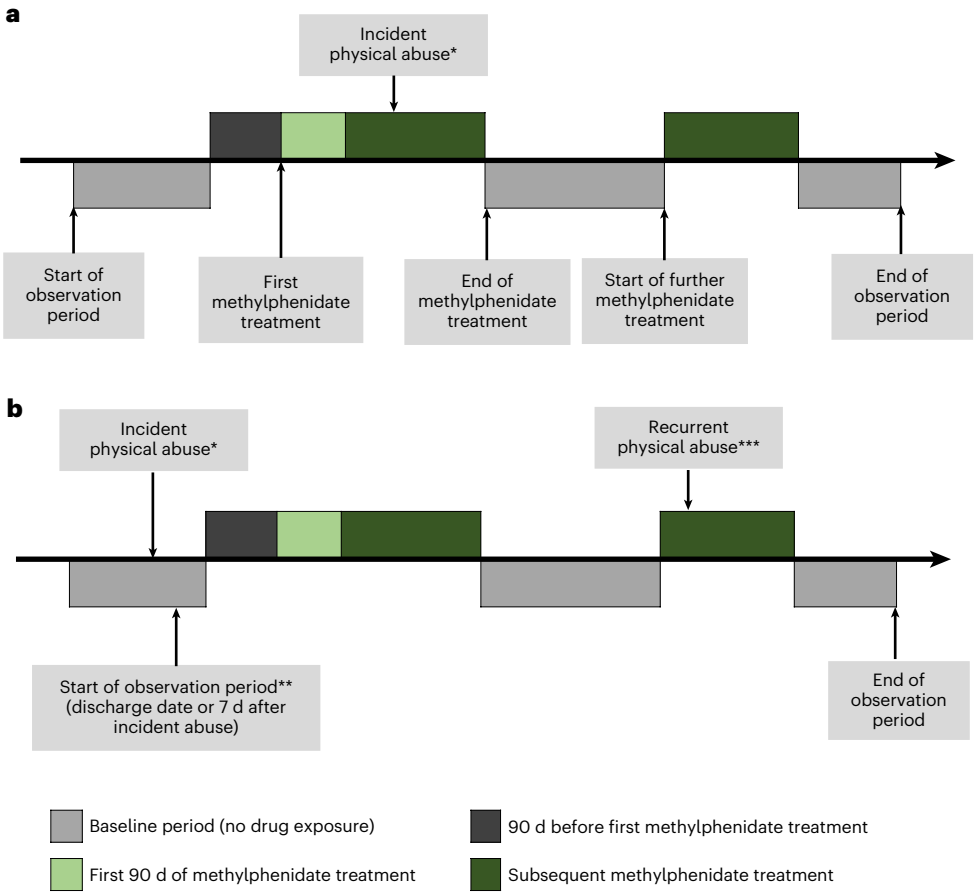

Fig. 1 | Illustration of SCCS study design. a, Outcome of incident physical abuse. **b**, First recurrent physical abuse. This is a hypothetical figure for an individual. *Incident case can occur at any time after or even before the observation start date. **New observation start date set as 1 January 2001, the child's 5th birthday, day 7 after the incident abuse or the discharge date of the incident abuse hospitalization episode, whichever was later. ***Recurrent case can occur at any time during the newly defined observation period.

another the responsibility sits with the perpetrator. Furthermore, it is a societal issue that requires assistance from the whole society, including but not limited to family-[15,16], school-[17,18] and community-based interventions[19] to provide mental health support for both children and caregivers. However, such a comprehensive network of social support is not available in many countries, including Hong Kong[20,21].

Direct training and support can help parents to become more competent in dealing with ADHD children, and to adopt a more supportive, empathetic and positive parenting style. This can improve parent–child relationships and reduce parental stress, thereby potentially leading to improved wellbeing and reduce rates of abuse for children with ADHD[22,23,24].

In addition, reducing ADHD symptoms in childhood may also be associated with reduced risk of abuse. Previous studies have suggested that medications for ADHD, such as the psychostimulant methylphenidate (MPH)[25,26], may lower the risk of physical injury[27–29]. This was hypothesized to be due to a reduction of core symptoms of impulsivity, inattentiveness and hyperactivity, which results in a decreased likelihood of involvement in accidents[27]. Despite some common side effects such as nausea, headache and stomach ache, MPH has been shown to have the best safety profile among ADHD medications[30]; recent meta-analyses and systematic reviews also add support for the efficacy of pharmacological treatments for ADHD in reducing core symptoms of the disorder[31,32]. In addition, a recent study[33] showed that MPH treatment had a positive effect on improving parent–child interactions and social cognition such as recognition of emotions and understanding of false belief among children with ADHD, through the oxytocin system. We therefore hypothesized that the use of pharmacological treatment for children with ADHD could lower the risk of physical abuse.

In view of the global increase in ADHD medication use[25,26,34] and the lack of research on the effects of ADHD medication on child physical abuse, the aim of this study was to evaluate the effect of MPH on the risk of physical abuse using advanced pharmacoepidemiological approaches[25,26].

Results

Following the self-controlled case series (SCCS) design (Fig. 1), we first identified 39,403 individuals aged 5–16 years with at least one MPH prescription, and finally included 1,064 patients with a first physical abuse event during the study period (Fig. 2), of which 818 (76.9%) were male and 246 (23.1%) were female. The overall incidence of physical abuse during MPH treatment was 3.53 per 1,000 patient-years. The mean (standard deviation) age at the start of the observation was 5.53 (1.57) years, and the mean duration of follow-up per participant was 8.48 (3.29) years. The mean MPH exposure was 2.59 (2.25) years per participant. Of the 1,064 patients with physical abuse, 867 (81.5%) had a recorded ADHD diagnosis. Broader psychiatric comorbidities for these patients are reported in Supplementary Table 1. Of the 1,064 first physical abuse events, 225 occurred during the MPH treatment and 839 occurred during the non-medicated period (Table 1). The median age of the index physical abuse event was 8.6 years (interquartile range, IQR, 7.0–10.7 years) (Extended Data Fig. 1). The crude incidences of physical abuse events in different risk windows are summarized in Table 2. There were three deaths during the study period.

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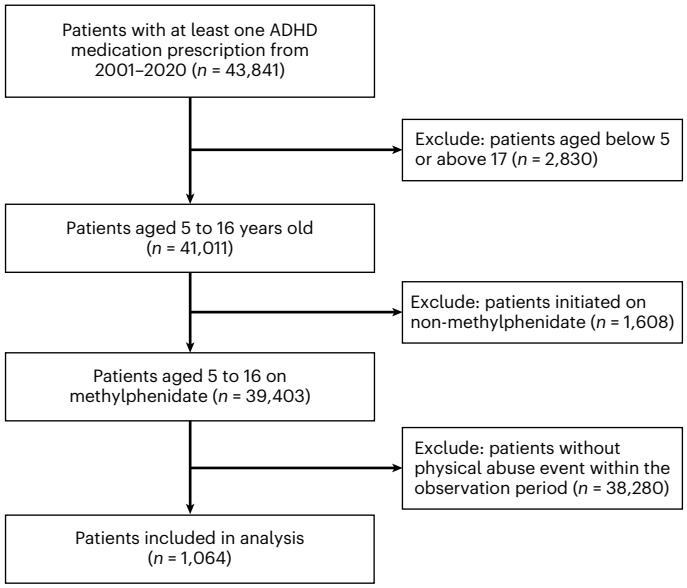

Fig. 2 | Flowchart of patient identification. This figure shows the inclusion and exclusion criteria of study cohort identification.

Risk of incident abuse

After adjusting for age, season and the COVID-19 stringency index, there was an increased risk of physical abuse during the 90 d period before MPH initiation (incidence rate ratio, IRR, 4.49; 95% confidence interval, CI, 3.76–5.36). The IRR was similar to baseline levels during the first 90 d of MPH treatment (IRR, 0.90; 95% CI, 0.63–1.29) and was lower than the baseline levels during prolonged MPH treatment (IRR, 0.63; 95% CI, 0.51–0.77) (Table 2). When directly compared with the pre-exposure period (Fig. 3), the risk of physical abuse was lowered by 80% during the first 90 d of MPH treatment (IRR, 0.20; 95% CI, 0.14–0.29) and by 86% in the subsequent MPH treatment period (IRR, 0.14; 95% CI, 0.11–0.18).

Risk of first recurrent physical abuse

A similar association was observed between MPH and recurrent physical abuse. We identified 219 children who had their first recurrent physical abuse events during the observation period, with 61 events occurring during the MPH treatment period (Table 2). Compared with the non-medicated period, we found an increased risk of recurrent physical abuse during the 90 d period before MPH initiation (IRR, 1.77; 95% CI, 1.08–2.90), slightly lower risk during the first 90 d of MPH treatment (IRR, 0.41; 95% CI, 0.16–1.03) and no differences during prolonged MPH treatment (IRR, 0.78; 95% CI, 0.51–1.20) (Table 2). The risk of recurrent physical abuse during the first 90 d of MPH treatment and during the subsequent MPH treatment period was lowered by 77% (IRR, 0.23; 95% CI, 0.09–0.61) and 56% (IRR, 0.44; 95% CI, 0.25–0.77), respectively, compared with the pre-exposure period (Fig. 3).

Sensitivity and negative control analyses

The sex-stratified results showed a similar pattern to the main analysis (Supplementary Table 2). No association was found in any risk window in the negative control analysis using diseases of the urinary system and eye infection as outcomes (Table 2, Fig. 3 and Supplementary Table 2). We also found a lower risk of physical abuse during the 90 d post-treatment period. After adjusting for additional time-varying factors, other psychiatric comorbidities and/or other psychotropic medication use, a decreased risk of physical abuse after treatment initiation compared with the short period before medication use remained (IRRs ranging from 0.14 to 0.20). For all types of child abuse and neglect (n = 1,123) the results were similar to the outcomes for the main analysis of physical abuse. Other sensitivity analyses showed similar results (Fig. 4 and Supplementary Table 3). The E-value analysis indicated that results were unlikely to be affected by unmeasured confounding factors (Supplementary Discussion).

Discussion

The incidence of physical abuse was 4.5 times higher during the 90 d period before the start of treatment with MPH, returned to a similar risk in the first 90 d of MPH treatment and decreased by around one-third during the subsequent treatment period compared with the other non-medicated period (reference period).

After initiation of MPH treatment, it is possible that the initial reduction in recorded child physical abuse is related to reduced contact with parents because of the disclosure or close monitoring by social care, education or healthcare professionals, rather than to the direct beneficial effects of MPH. However, we observed that the IRR of child physical abuse was lower with a longer duration of use (>90 d) beyond the initial separation period. Therefore, it is unlikely that our results are fully explained by the increased monitoring associated with the initiation of MPH.

To further examine the sensitivity of our results to any changes in surveillance of child physical abuse, we conducted an analysis to study the risk of first recurrent physical abuse events corresponding to the use of MPH. The results follow a similar pattern of risk to that observed in the main analysis. This subgroup analysis showed that, even in a group of children who were already under close surveillance due to previous history of abuse, there was still a higher risk of physical abuse directly before MPH initiation but not in other risk periods. Such findings further support the association between MPH treatment and lower risk of physical abuse beyond the potential effects of close surveillance by professionals.

Several factors may explain why the period before the initiation of MPH treatment coincides with higher incidence of physical abuse. The highest risk of physical abuse in children during the pretreatment period might be a trigger for screening, diagnosis and treatment engagement of ADHD. In clinical practice, the initiation of new medication often occurs when there are specific concerns about the child's mental and physical health. The decision to start MPH treatment in these patients may be in response to changes in behavioural or related psychiatric problems associated with physical abuse events. In contrast, the negative control analysis using diseases of the urinary system and eye infection, which should not be associated with ADHD or MPH treatments, did not show the same risk patterns as in the primary or subgroup analyses. Furthermore, the robustness of the primary analyses was supported by the sensitivity analyses.

Previous studies have demonstrated that, when ADHD symptoms in children are reduced by medication, there is an associated reduction in parental stress, less negative parenting and improved parent–child relationships[33,35,36], which can potentially reduce the risk of physical abuse. However, it is important to proactively address ways in which to bolster support for parents, for example, via parental training programmes[37–40] to improve the quality of parenting and reduce parental stress levels, as well as incorporating resources via schools[17,18] and community centres[19].

The availability of psychosocial interventions is inconsistent and, if available, they are mostly focused on addressing children's symptoms with a behavioural training approach[21,41,42]. It is widely acknowledged that there is a very limited availability of evidence-based behavioural parent training programmes in the publicly funded healthcare system in Hong Kong for parents of children with ADHD. Two previous research studies have shown that parenting stress ratings remained unchanged after attending a local parental training programme, 'Multifamily Therapy for Children With ADHD'[42,43].

Despite multiple studies on MPH incorporating real-world outcomes, there have been few examinations of potential effect on the risk of child physical abuse. Studies from Scandinavia and

Table 1 | Patient characteristics

	No. of patients (%)	Mean age at baseline (years) ± s.d.	Median daily dosage (IQR) (mg)	Median length of prescription (IQR) (d)	Exposed period		Unexposed period	
					No. of events	Total follow-up time (patient-years)	No. of events	Total follow-up time (patient-years)
All	1,064 (100)	5.53±1.57	10 (10–20)	69 (34–111)	225	2,767.98	839	6,256.47
Male	818 (76.9)	5.56±1.60	10 (10–20)	70 (39–111)	178	2,162.09	640	4,731.29
Female	246 (23.1)	5.44±1.45	10 (10–20)	69 (27–111)	47	605.89	199	1,525.18

Table 2 | Results from the SCCS analysis

Treatment	Risk window	Number of events	Patient-years	Crude incidence (in 100 patient-years)	IRRs*	95% CIs		*P*
Primary analysis								
Incident physical abuse (*n*=1,064)								
MPH	90 d before treatment	181	252.02	71.82	4.49	3.76	5.36	<0.001
	First 90 d of treatment	34	221.16	15.37	0.90	0.63	1.29	0.57
	Subsequent treatment	191	2546.83	7.50	0.63	0.51	0.77	<0.001
	No MPH (reference)	658	6,004.45	10.96	1.00	1.00	1.00	—
First recurrent physical abuse (*n*=219)								
MPH	90 d before treatment	22	43.27	50.84	1.77	1.08	2.90	0.02
	First 90 d of treatment	5	39.29	12.73	0.41	0.16	1.03	0.06
	Subsequent treatment	56	524.64	10.67	0.78	0.51	1.20	0.26
	No MPH (reference)	136	811.36	16.76	1.00	1.00	1.00	—
Negative control analysis								
Diseases of the urinary system (ICD-9-CM: 580–599) (*n*=514)								
MPH	90 d before treatment	17	123.34	13.78	1.08	0.66	1.78	0.75
	First 90 d of treatment	17	105.36	16.14	1.31	0.80	2.17	0.28
	Subsequent treatment	110	1,194.38	9.21	1.10	0.84	1.46	0.48
	No MPH (reference)	370	3,254.37	11.37	1.00	1.00	1.00	—
Eye infection (ICD-9-CM: 370, 373, 363.0–363.2, 372.0–372.3) (*n*=929)								
MPH	90 d before treatment	33	224.57	14.69	1.12	0.78	1.60	0.54
	First 90 d of treatment	25	190.27	13.14	0.99	0.66	1.50	0.98
	Subsequent treatment	194	2,193.23	8.85	0.95	0.77	1.16	0.61
	No MPH (reference)	677	6,147.10	11.01	1.00	1.00	1.00	—

*All estimates were adjusted for age in 1-year age band and seasonal effect, and COVID-19 stringency index using conditional Poisson regression, with a significance level of 5% for a two-tailed test. ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

Hong Kong have reported that MPH not only improves ADHD symptoms[31], but is also associated with lower risks of other more distal outcomes such as motor vehicle accidents[44], traumatic brain injury[45], substance use disorder[46], criminality[47] and more general functional outcomes[48]. A previous network meta-analysis[31] has demonstrated that MPH can reduce ADHD core symptoms across different age groups. Therefore, it might be reasonable to assume that the effects of MPH on the risk of physical abuse could also be observed in other age groups.

It is worthwhile to note that, despite a well established safety profile, some children treated with MPH can experience side effects such as increased blood pressure, increased heart rate and poor appetite[49,50]. However, research has shown that these side effects are unlikely to be severe and can often be managed by changing the dose, timing of dose and/or formula of the medication; clinicians and parents should monitor if they continue to cause problems to the children and look at other options if necessary[51,52].

Limitations

There are several limitations to our study. First, the data source—Clinical Data Analysis and Reporting System (CDARS)—used in this study only includes information from public hospitals or clinics, without cases seen by private medical practitioners. However, in Hong Kong, the public sector is the main provider of specialist care and there are only a few private child psychiatrists[27,53,54]. Therefore, the vast majority of patients receiving MPH should be included in this study. Another limitation is that our cohort included only clinically referred patients who had sufficiently severe ADHD symptoms to receive MPH treatment. Therefore, our cohort may have a higher baseline risk of physical abuse compared with non-medicated patients. However, since we applied the within-individual design—SCCS—the individual baseline risk should not affect our results and conclusion. Similarly, identifying child physical abuse cases using hospital records may result in an underestimation of numbers, as only severe cases would be hospitalized. Again, due to the nature of the SCCS design, this would only affect statistical power

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Risk window	Number of events	Patient-years	Crude incidence#	IRRs* (95% CIs)	P-value
Primary analysis					
Incident physical abuse (*n* = 418)					
First 90 d of treatment	39	233.42	16.71	0.20 (0.14–0.29)	<0.001
Subsequent treatment	192	2,649.36	7.25	0.14 (0.11–0.18)	<0.001
90 d before treatment	187	265.84	70.34	1.00 (—)	—
First recurrent physical abuse (*n* = 90)					
First 90 d of treatment	5	42.77	11.69	0.23 (0.09–0.61)	0.003
Subsequent treatment	63	580.42	10.85	0.44 (0.25–0.77)	0.004
90 d before treatment	22	46.89	46.92	1.00 (—)	—
Negative control analysis					
Diseases of the urinary system[a] (*n* = 144)					
First 90 d of treatment	17	105.36	16.14	1.21 (0.62–2.38)	0.57
Subsequent treatment	110	1,194.4	9.21	1.02 (0.60–1.73)	0.94
90 d before treatment	17	123.34	13.78	1.00 (—)	—
Eye infection[b] (*n* = 252)					
First 90 d of treatment	25	190.27	13.14	0.89 (0.53–1.50)	0.66
Subsequent treatment	194	2,193.23	8.85	0.85 (0.58–1.24)	0.40
90 d before treatment	33	224.57	14.69	1.00 (—)	—

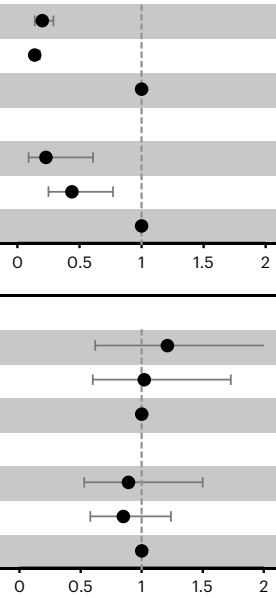

Fig. 3 | Results of direct comparison (90 d before treatment as reference group) from SCCS analysis. [a]ICD-9-CM: 580–599. [b]ICD-9-CM: 370, 373, 363.0–363.2, 372.0–372.3. This figure visually summarizes the IRRs and 95% CIs. *All estimates were adjusted for age in one-year age band and seasonal effect, and COVID-19 stringency index using conditional Poisson regression, with a significance level of 5% for a two-tailed test. The error bars represent the corresponding 95% CIs of the IRRs. #In 100 patient-years.

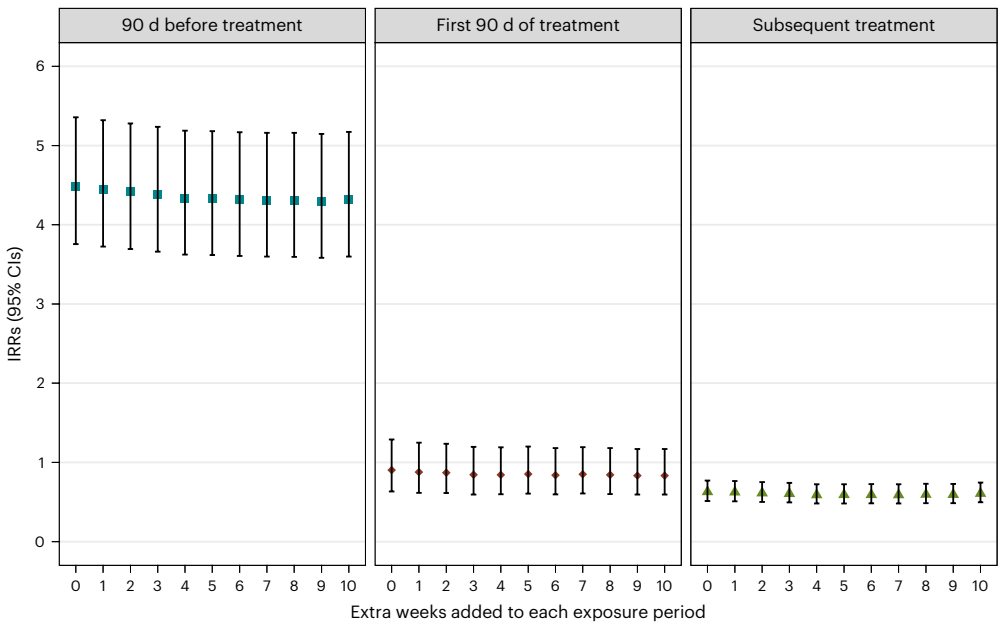

Fig. 4 | Sensitivity analysis on exposure periods by adding 1–10 weeks after the end of an exposed period: IRRs of physical abuse in each risk window. *n* = 1,064. Data are presented as IRRs and 95% CIs, which were adjusted for age in one-year age band and seasonal effect, and COVID-19 stringency index using conditional Poisson regression, with a significance level of 5% for a two-sided test.

rather than the interpretation of the result. Nevertheless, our results may not be applicable to children with mild ADHD who do not require pharmacological treatment. Additionally, as we included a comparatively long follow-up period, time-varying confounding factors might influence study results. However, in addition to the adjustment of major time-varying confounders, age and seasons, we conducted sensitivity analyses by adjusting for various time-varying confounders including psychiatric comorbidities and medication use that did not yield any major changes in the results. Finally, the *E* values in our sensitivity analysis indicated that our estimates could only be explained by such confounding effects if they were associated with both treatment and outcome at a magnitude of 9.47–13.77-fold, respectively, in addition

to the confounders already addressed. Any residual confounding is unlikely to exert such powerful effects on our study conclusions.

Conclusion

Results from the main analysis and sensitivity analyses are consistent with our hypothesis that the use of MPH for ADHD is associated with a lower risk of physical abuse. Medications could play an important role as part of the support package for families raising children with ADHD, creating a positive effect that could last during treatment and beyond.

Methods

Data source

This study used data from CDARS, the electronic health records database developed by the Hong Kong Hospital Authority, a statutory body that manages all public hospitals and their ambulatory clinics in Hong Kong. The Hospital Authority health services are available to all Hong Kong residents (over 7.4 million people) and cover about 80% of all hospital admissions in Hong Kong[55]. Data from CDARS have been validated and used in a variety of pharmacoepidemiological studies[54,56,57]. Patient-specific data in CDARS include diagnoses, hospital admissions/discharges and prescription/dispensing information[58]. The study protocol was approved by the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference no. UW 12–136). This was a pharmacoepidemiology study without patient contact and therefore informed consent was exempted.

SCCS design

We used an SCCS design[59,60] to investigate the association between MPH use and child physical abuse. We have previously used SCCS to investigate the effects of MPH on various conditions[27,53,54,57], in which patients served as their own controls and comparisons were made within individuals who experienced both the outcome and the exposure of interest[59]. IRRs were derived by comparing the rate of events during medication exposure with the rate during non-medicated periods using conditional Poisson regression. The major advantage of SCCS design over conventional study designs (for example cohort design) is that it implicitly controls for measured and unmeasured time-invariant confounders that vary between individuals, such as genetic factors, socioeconomic status and underlying disease severity[59]. Furthermore, we adjusted for time-varying factors, including age, season and the COVID-19 stringency index in the main analysis as well as other mental disorders and other psychotropic medications in the sensitivity analyses, which potentially affect MPH prescribing[34,61]. As the COVID-19 pandemic has severely affected daily life, the COVID-19 stringency index[62], an indicator that reflects the toughness of various regions in response to COVID-19, with a higher index representing a more stringent response measure, was further adjusted as another time-varying factor. Within-individual approaches such as the SCCS design have become a common methodology in ADHD medication research over the past decade[63]. Details of the SCCS assumptions relevant to the current study are available in Supplementary Note 1, Extended Data Fig. 2 and Supplementary Table 4.

Case identification

Children aged 5–16 years who had received at least one MPH prescription and experienced an incident physical abuse event during the study period (1 January 2001 to 31 December 2020) were identified from CDARS. The outcomes of physical abuse were identified using the ICD-9-CM diagnostic codes: E967 (perpetrator of child and adult abuse, external causes of injury and poisoning) and 995.54 (child physical abuse). Child physical abuse is strictly defined as any act of commission that endangers or impairs the physical health and development of a child[64]. While under the care of the Hong Kong Hospital Authority, for every case admitted for suspected child abuse, a multidisciplinary case conference is held within 10 working days after the case report to investigate the results and evidence from different parties within the context of the child and family to confirm case details and plan intervention[64]. The ICD-9-CM code of physical abuse will only be added after the decision is made by the conference as a statutory requirement, and therefore the recorded diagnosis extracted from CDARS has very high validity. We included all MPH users, regardless of whether they had a record of ADHD diagnosis, because MPH is almost exclusively used in children for the management of ADHD in Hong Kong. MPH is currently not licensed for narcolepsy in Hong Kong for children and the incidence of narcolepsy is between 25 and 50 per 100,000 people[65]. Hence MPH is very unlikely to be used for narcolepsy. Furthermore, the aim of this study was to evaluate the association between MPH use and risk of physical abuse, and such a definition for MPH exposure had been used in previous studies[66,67]. Atomoxetine was the only other licensed treatment for ADHD in Hong Kong and use was minimal during the study period[34]; thus observation periods were censored by atomoxetine treatment to avoid coprescribing situations that would affect the comparisons.

We commenced follow-up at 5 years of age as MPH is not recommended for children below this age[68]. Individual observation periods began on 1 January 2001 or on the child's fifth birthday, whichever was later, and ended on 31 December 2020, on the child's 17th birthday or on the registered date of death, whichever was earliest.

Exposures and outcomes

For each study subject, all MPH prescriptions and abuse events were identified. Exposure periods were defined as the time of receiving MPH, and the duration between prescription start and end dates was recorded in CDARS for each prescription as a time-varying variable. More than 99% of the prescriptions recorded start and end dates. Daily dosage and the quantity prescribed were used to determine the duration of treatment if the prescription end date was not available. Median values for the exposure duration were imputed when the above information was missing. We divided the patient-time into four discrete windows: (1) 90 d before the first MPH exposure (pre-exposure period), (2) first 90 d of MPH use, (3) subsequent MPH use (>90 d) and (4) baseline period (the patient-time that falls outside the three previously stated categories, including patient-time before pre-exposure and after completing MPH). The corresponding date of the abuse was identified as the event date. The study design and timeline for a single hypothetical participant are illustrated in Fig. 1a.

Statistical analysis

Risk of incident abuse. The association between MPH use and childhood physical abuse was calculated by comparing the rates of physical abuse during exposure and non-exposure periods. Adjusted IRRs and the corresponding 95% CIs were calculated and adjusted by age in 1-year bands, seasonal effects and COVID-19 stringency. A 90 d pre-exposure period was added to account for the possibility that a recent physical abuse event may affect the likelihood of MPH treatment, which in turn may introduce bias into the risk estimate during treatment. We separated the first 90 d of MPH use to allow detection of any temporary changes in the risk of physical abuse; we also compared the rate of physical abuse between the pre-exposure period and MPH-exposed periods. Stratified analyses were conducted to evaluate the effects by sex.

Risk of first recurrent physical abuse. To evaluate the risk of subsequent physical abuse during MPH treatment in those children who were already under vigilant surveillance after the physical abuse event, we further investigated the association between MPH and the risk of first recurrent physical abuse. Children with a history of physical abuse where the first recurrent physical abuse events were recorded during the individual's observational period were included. The follow-up period began on 1 January 2001, the child's fifth birthday, day 7 after

the incident physical abuse or the discharge date of the incident physical abuse hospitalization episode, whichever was latest, and the IRR of the subsequent physical abuse was evaluated during the different exposure windows using the same definition and analysis as outlined above (Fig. 1b).

Sensitivity and negative control analyses. Sensitivity analyses were conducted to test the validity and robustness of the initial study results: (1) different drug non-adherence scenarios, (2) redefining the start of the observation as the latest of the first observed date of ADHD diagnosis/MPH treatment, (3) restriction to incident users of MPH, (4) >120 d of MPH exposure, (5) restricting the study period to 31 December 2019 to reduce the impact of COVID-19 on the results, (6) adding a 90 d post-exposure period, (7) adjusting for other comorbid psychiatric disorders, (8) adjusting for both other comorbid psychiatric disorders and other psychotropic medication use, (9) including all types of child abuse and neglect as the outcome, (10) two negative controls using diseases of the urinary system (ICD-9-CM: 580–599) and eye infection (ICD-9-CM: 370, 373, 363.0–363.2, 372.0–372.3) as alternative outcomes and (11) further assessment of the potential impact of any unmeasured confounders by computing the *E* value[69]. Detailed descriptions of these analyses are available in Supplementary Note 2.

A two-tailed *P* value of 0.05 was used in all statistical analyses. R4.0.3 was used for data manipulation and analyses. We have reported the results according to the Strengthening the Reporting of Observational Studies in Epidemiology Statement. According to the formula suggested by Musonda et al.[70], our sample size of 1,064 is able to detect an IRR of 0.826 at 5% of significance and 80% power (detailed information on the formula and the exact calculation is shown in Supplementary Equation).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Data cannot be shared as the data custodian—Hong Kong Hospital Authority—did not give permission due to patient confidentiality and privacy concerns. According to the conditions laid down by Hong Kong Hospital Authority, only local academic institutions, government departments or non-governmental organizations may apply for access to data through the Hospital Authority data sharing portal (https://www3.ha.org.hk/data).

Code availability

All relevant analysis codes are available online (https://github.com/legao513/child-abuse).

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Author contributions

K.K.C.M., L.G., P.I. and I.C.K.W. designed the study. K.K.C.M., L.G., W.C.Y.L. and M.F. extracted the data, conducted the statistical analyses and cross-checked the analyses. K.K.C.M. and L.G. wrote the first draft of the manuscript. D.C. and P.I. provided critical input to the interpretation of the analyses. P.I. and I.C.K.W. are the principal investigators, providing resources and supervising all aspects of the project. All authors contributed to the interpretation of the analyses and the review and editing of the manuscript, and approved the submission of the final version.

Competing interests

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Additional information

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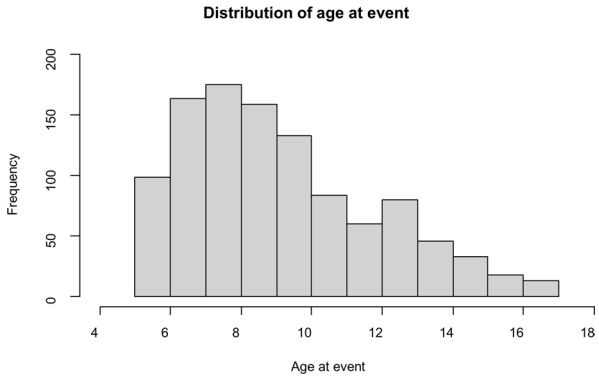

Extended Data Fig. 1 | Histogram of age at the incident physical abuse.

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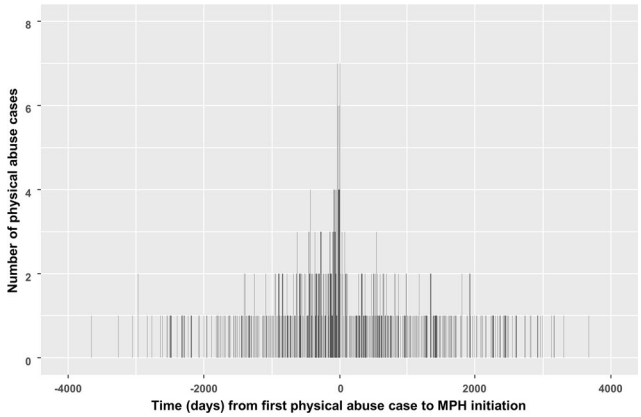

Extended Data Fig. 2 | Time from the first physical abuse case to MPH initiation. Abbreviation: MPH, methylphenidate.

nature research

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	The tool (Clinical Data Analysis and Reporting System) developed by Hong Kong Hospital Authority was used to retrieve data.
Data analysis	R4.0.3 was used for data manipulation and analyses. All relevant analysis codes are available online (https://github.com/legao513/child-abuse).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

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Data can not be shared as the data custodian – HK HA did not give permission due to patient confidentiality and privacy concerns. Local academic institutions, government departments, or non-governmental organizations may apply for the access to data through the Hospital Authority's data sharing portal (https://www3.ha.org.hk/data).

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Life sciences study design

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Sample size	According to the formula suggested by Musonda et al., our sample size of 1,064 is able to detect an IRR of 0.826 at 5% of significance and 80% power.
Data exclusions	Patients aged below 5 or above 17 (We commenced follow-up at 5 years of age as MPH is not recommended for children below this age.) Patients initiated on non-methylphenidate (Atomoxetine was the only other licensed treatment for ADHD in HK and use was minimal during the study period; thus observation periods were censored by atomoxetine treatment to avoid co-prescribing situations that would affect the comparisons.) Patients without physical abuse within the observation period
Replication	The analyses have been been conducted independently by four authors, reached exactly the same results. Local academic institutions, government departments, or non-governmental organizations may apply for the access to data through the Hospital Authority's data sharing portal (https://www3.ha.org.hk/data) and replicate this analysis.
Randomization	NA. This is a retrospective observational study using real-world electronic health records, so randomization is not applicable for this study.
Blinding	NA. This is a retrospective observational study using real-world electronic health records, so blinding is not applicable for this study.

Reporting for specific materials, systems and methods

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☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	Among 39,403 individuals aged 5 to 16 years with at least one MPH prescription, 1,064 patients had a first physical abuse event during the study period, of which 818 (76.9%) were male and 246 (23.1%) were female. The overall incidence of physical abuse during MPH treatment was 3.53 per 1,000 patient-years. The mean (standard deviation) age at the start of the observation was 5.53 (1.57) years, and the mean duration of follow-up per participant was 8.48 (3.29) years. The mean MPH exposure was 2.59 (2.25) years per participant. Of the 1,064 patients with physical abuse, 867 (81.5%) had a recorded ADHD diagnosis. Broader psychiatric comorbidities for these patients are reported in Supplementary Table 1.
Recruitment	This is a retrospective observational study using real-world electronic health records, so we directly extracted patient records from the electronic databases by their demographics (age 5-16), prescription records (MPH) and diagnosis (experienced an incident physical abuse event) during the study period (1 January 2001 to 31 December 2020). Potential bias: 1.CDARS does not link data from cases seen by private medical practitioners. However, in HK, the public sector is the main provider of specialist care and there are only a few private child psychiatrists.Therefore, the vast majority of patients receiving MPH should be included in this study. 2. This cohort included only clinically referred patients who had sufficiently severe ADHD symptoms and/or impairment to

	receive MPH treatment. Therefore, our cohort may have a higher baseline risk of physical abuse compared with non-medicated patients. However, since we applied the SCCS design, the individual baseline risk should not affect our results and conclusion. Similarly, identifying child physical abuse cases using hospital records may result in an underestimation of numbers as only severe cases would be hospitalized. Again, due to the nature of the SCCS design, this would only affect statistical power rather than the interpretation of the result.
Ethics oversight	The study protocol was approved by the institutional review board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference No. UW 12-136). This is a pharmacoepidemiology study without patient contact and therefore informed consent is exempted.

Note that full information on the approval of the study protocol must also be provided in the manuscript.